## REMARKS

Following entry of the foregoing amendments, claims 38, 40, and 61 will be pending in this patent application. Claim 61 has been amended herein, without prejudice. No new claims have been added, and no claims have been canceled. Support for the amendments is found throughout the specification as originally filed, including, for example, experimental examples 3 and 4 at page 83, lines 10 to 12 and page 83, line 34, and the amendments thus do not introduce new matter into the application.

Applicants respectfully request reconsideration of the rejections of record in view of the foregoing amendments and the following remarks.

### Alleged Obviousness

Claims 38, 40, and 61 have been rejected under 35 U.S.C. § 103(a) as allegedly rendered obvious by U.S. patent application publication number 2004/019626 ("the McSwiggen application") in view of U.S. patent application publication number 2003/0166282 ("the Brown application"), and have been independently rejected as allegedly rendered obvious by the McSwiggen application in view of U.S. patent application publication number 2005/0181382 ("the Zamore application"). If the Office considers these rejections to apply to the claims as amended herein, applicants respectfully request reconsideration and withdrawal thereof, because the presently claimed complementary oligonucleotides would not have been obvious to those of ordinary skill in the art at the time of the invention in light of the high degree of unpredictability in the art at that time.

Under the "obvious to try" standard for assessing obviousness, which the Office appears to have applied in the present case, claimed subject matter would have been obvious if the subject matter could have been arrived at by simply choosing from among a finite number of identified, predictable solutions, with a reasonable expectation of success.[1] Such an approach could not have been used to develop the presently claimed complementary oligonucleotides,

[1] M.P.E.P. § 2143 E.

however, and duplexes of the oligonucleotides therefore would not have been obvious before applicants' invention.

The claims have been amended herein to recite, *inter alia*, compositions comprising duplexes consisting of complementary antisense and sense oligonucleotides in which the antisense oligonucleotide is complementary to a target nucleic acid, each nucleoside of the antisense oligonucleotide comprises a 2'-fluoro modification, each guanine of the natural sequence of the sense oligonucleotide is substituted with an inosine, and the sense oligonucleotide comprises at least one inosine. The claims further recite that the duplexes reduce the level of target nucleic acid present in a cell by at least 63 %.

The art of RNA interference was unpredictable at the time of the invention, and those of ordinary skill in the art accordingly could not have anticipated at that time which motifs of chemical modifications present in duplexes of complementary oligonucleotides would have yielded compounds that reduce the level of target nucleic acid present in a cell by at least 63 %. In this regard, the presently claimed duplexes represent a selection from among a nearly infinite number of *unpredictable* possible choices. Moreover, in light of the unpredictability in the art at the time of the invention, those of ordinary skill would not have reasonably expected at that time that the claimed complementary oligonucleotides could have been successfully used for RNA interference.

More specifically, as discussed at length in the previous response, which discussion will not be repeated here, the cited references describe a virtually limitless number of patterns and combinations of chemical modifications that could be present in siRNA molecules. In addition, at the time of the invention, those of ordinary skill in the art could not have predicted with a reasonable degree of certainty whether a given duplex of complementary chemically modified oligonucleotides would exhibit RNA interference activity. The design and production of biologically active siRNAs was accordingly highly unpredictable at that time. To this end, it was known in the art before applicants' invention that "not all siRNA molecules designed to hybridize to an RNA transcript are effective."[2] Accordingly, at the time of the invention, those

[2] Vickers, T.A., *et al.*, *J. Biol. Chem.*, 2003, 278, 7108-7118, attached as Exhibit A.

of ordinary skill in the art could not have reasonably predicted whether a given double-stranded RNA molecule would exhibit RNA interference activity, much less reduce the level of target nucleic acid present in a cell by at least 63 %.

In light of this unpredictability in the art, those of ordinary skill would not have reasonably expected that a particular chemically modified siRNA molecule, other than the siRNAs specifically reported in the art to have been produced and tested for biological activity, would have been active in RNAi. Those skilled in the art accordingly would not have had a reasonable expectation before applicants' invention that the claimed chemically modified complementary oligonucleotides would reduce the level of target nucleic acid present in a cell by at least 63 %, in light of the highly unpredictable state of the art. With respect to this unpredictability in the art, the Office asserts that "[w]hile it is correct that one cannot predict activity [of an siRNA] *a priori*, the examiner notes that the instant claims do not require an degree of activity."[3] As discussed above, however, the claims have been amended herein to recite that the complementary oligonucleotides reduce the level of target nucleic acid present in a cell by at least 63 %.

Viable solutions to the problem of developing stable, biologically active siRNA molecules could not have been reasonably predicted based upon the state of the art at the time of the invention. In light of this unpredictability in the art, those skilled in the art would not have had a reasonable expectation of success for the claimed duplexes of chemically modified oligonucleotides before applicants' invention. The claimed compositions would therefore not have been obvious at that time, and applicants accordingly, respectfully, request withdrawal of the rejections for alleged obviousness.

[3] Office action dated December 9, 2009.

## Conclusion

Applicant believes that the foregoing constitutes a complete and full response to the official action of record. Accordingly, an early and favorable action is respectfully requested.

Respectfully submitted,

Date: March 5, 2010

/Jane E. Inglese/
Jane E. Inglese, Ph.D.
Registration No. 48,444

Woodcock Washburn LLP
Cira Centre
2929 Arch Street, 12th Floor
Philadelphia, PA 19104-2891
Telephone: (215) 568-3100
Facsimile: (215) 568-3439